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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/653,812	09/01/2000	Haig H. Kazazian JR.	9596-23U3	6101

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/653,812	KAZAZIAN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,36-44,46,47 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,36-44,46,47 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed March 23, 2005 (hereinafter referred to as "the response") has been entered. Claim 34 has been amended.

Claims 34, 36-44, 46, 47, and 49 remain pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 23, 2005 has been entered.

Oath/Declaration

The oath or declaration filed March 23, 2005 is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

> It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

A preliminary amendment was filed September 1, 2000 in this divisional application. The declaration does not specifically refer to the amendment. See the objection to the declaration at page 2 of the Office Action of 12/17/01, the declaration subsequently filed on 6/12/02, and the declaration filed 3/23/05. A newly executed declaration is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 36-44, 46, 47, and 49 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in the Office Actions of 12/17/01 and 9/22/04, and for the reasons discussed herein, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a transgenic mouse comprising a specific retrotransposon, as well as a sperm cell obtained from a male transgenic mouse comprising said specific retrotransposon. The claims cover transgenic mice having any gene inserted as well as those having any gene disrupted.

At pages 7-8 of the response, Applicants assert that the specification provides many uses for the claimed transgenic mouse and that all these uses are enabled.

At page 7, paragraph 1 of the response, Applicants point to the specification at page 16, beginning at line 7, and assert that the cited section describes a use for the transgenic animal "for random insertional mutagenesis in the animal." It does not. The cited section only refers to a use for the **retrotransposon element**, not for the claimed transgenic mouse. The cited section does not mention a transgenic animal at all. Nowhere does the specification describe how **an animal** can be used to effect random insertional mutagenesis in an animal. Such a use does not make sense. Moreover, the paragraph Applicants cite only describes a use for the L1 retrotransposon element, not an animal, stating that "these

retrotransposons may be used for random insertional mutagenesis" (page 16, lines 19-20). The cited paragraph does not contemplate a use for the claimed transgenic mouse.

At page 7, paragraph 1 of the response, Applicants point to the specification at page 20, beginning at line 24, and assert that the cited section discloses the use of a transgenic animal comprising a DNAc molecule useful for generating mutations in a cell and for the generation of transposon mutagens. Again, only the DNA molecule is "useful for generating mutations in a cell and for the generation of transposon mutagens," not the animal. The animal cannot be used to generate mutations in the cell or to generate transposon mutagens. The cited paragraph states that "[e]ngineered L1 elements can also be used as transposon mutagens." Obviously, the claimed **transgenic mice** cannot be used for the generation of transposon mutagens. The cited paragraph also states that the DNAs of the invention are useful for generating transgenic animals having insertional mutations, contrary to Applicants present assertion that the **animals** would be used to to generate mutations. There is nothing in the specification that suggests that transgenic mice can be used to actually generate mutations. The cited paragraph does not contemplate a use for the claimed transgenic mouse.

At page 7, paragraph 1 of the response, Applicants point to the specification at page 27, line 22, and assert that the specification describes "*using* transgenic mice comprising a DNAc molecule for generating high frequency mutation" (emphasis original). Of course, it is the DNAc molecule that is used to generate high frequency mutations, not the transgenic mouse. The cited paragraph only describes how to make transgenic mice of the invention. There is nothing in the cited paragraph that refers to a use for the claimed transgenic mice.

At page 7, paragraph 1 of the response, Applicants point to the specification at page 28, beginning at line 4, and assert that "this high frequency mutation can be *used* to provide mutations in a variety of genes, including genes which provide resistance or susceptibility to tumor development" (emphasis original). Applicants conclude that the skilled artisan could "*use* the transgenic mammal and

the sperm presently claimed to illuminate the function of various genes in which the DNAc molecule integrated" (emphasis original). The cited paragraph does not contemplate a use for the claimed transgenic mice, but rather states that "promoter traps or enhancer traps in somatic cells may be used to provide mutations in a variety of genes, including, but not limited to genes which provide susceptibility or resistance to tumor development in various cell types." Indeed, the transgenic mouse described in the specification (page 27, line 22 to page 28, line 3) would have many mutations within a single mouse, including the initial germline genetic modification, followed by many somatic cell modifications, so that the resulting mouse would be a mosaic animal having different mutations in different cells and tissues. Nowhere does the specification teach how to use such a mouse to identify genes which provide resistance or susceptibility to tumor development. The cited paragraph does not teach how to use the claimed transgenic mouse to identify genes which provide susceptibility or resistance to tumor development in various cell types and furthermore does not teach how to use the claimed transgenic mouse "to illuminate the function of various genes in which the DNAc molecule integrated," as Applicants allege.

At page 7, paragraph 1 of the response, Applicants point to the specification at page 28, beginning at line 8, and assert that the transgenic mouse of the invention is particularly useful for discovering gene function because "only one copy of the gene integrates into any specific chromosomal location, allowing specific analysis of one mutation on the rest of the transgenic mouse's biological functions, rather than a less specific 'shotgun' approach that may result in no control over the number of copies integrated into the genome." While it may be true that "only one copy of the gene integrates into any specific chromosomal location" as Applicants allege, the argument goes awry in the next clause where Applicants conclude that this allows "specific analysis of **one mutation**" (emphasis added), because nothing could be further from the truth. Applicants arguments are quite contrary to the teachings of the specification. The specification is replete with emphasis on how the L1 element can be used to generate "high frequency mutation" (e.g., page 27, line 29). The specification is clear that the

retrotransposon can be expected to insert randomly into **multiple loci** throughout the genome and the section of the specification that Applicants are referring to at page 28, describes the generation of transgenic mice that will have many mutations in a single mouse, mostly somatic cell mutations, because, as the specification explains, "this approach will lead to **high frequency mutation** during embryonic development and **post-natal life**" (page 27, line 29 to page 28, line 1, emphasis added). Thus, the specification is clearly describing transgenic mice in which high frequency mutation in post-natal life leads to a single animal that is a mosaic, have many different mutations in different somatic cells throughout the animal body. Thus, Applicants assertion that the transgenic mice allow the specific analysis of **one mutation** is contrary to the teachings of the specification.

At page 7, paragraph 2 of the response, Applicants point to the specification at page 33, beginning at line 10, and assert that it enables "*using* the transgenic mouse and sperm of the present invention for transposon mutagenesis experiments" (emphasis original). However, the cited section does not describe a use for the transgenic mice of the invention, but instead describes how to make transgenic mice that have a human L1 element integrated into a pre-determined site within the mouse genome. The "transpon mutagenesis" mentioned simply refers to the production of a mutation through the integration of the transposon into the mouse genome, in this case a site-specific integration. There is nothing in the cited paragraph that refers to a use for the claimed transgenic mice.

At page 7, paragraph 2 of the response, Applicants point to the specification at page 37, line 3, and assert that the specification "describes how to *use* the present invention to generate a library of cells comprising a knockout or mutated gene" (emphasis original). However, the "present invention" is the transgenic mouse, and a transgenic mouse cannot be used to generate a library of cells comprising a knockout or mutated gene; it is the **L1 element** that is used to create a library of cells comprising a knockout or mutated gene, **not the transgenic mouse.** There is nothing in the cited paragraph that even refers to a transgenic mouse.

At page 7, paragraph 2 of the response, Applicants point to the specification at page 38, and assert that the specification describes the use of transgenic mice in developing transgenic breeder stocks, which are useful in elucidating animal and gene function and evaluation of targets for gene therapy or classical drug intervention. However, while such a use is contemplated, there is nothing in the specification that teaches how to use the claimed transgenic mouse to evaluate targets for gene therapy or classical drug therapy. Therefore, such a use is not enabled by the instant specification. Furthermore, using transgenic animals to "study gene function" does not constitute a **specific and substantial** asserted utility within the meaning of 35 U.S.C. 101 because such a use constitutes carrying out further research on the product made, i.e. the transgenic mouse. See the prior Office Action of 9/22/04 at page 5, which explains that utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not **substantial** utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility. In this case, the asserted utility to "study gene function" is not **substantial** because it constitutes carrying out further research on the claimed product itself.

At page 8, paragraph 1 of the response, Applicants point to the specification at page 38, beginning at line 27, and assert that the specification provides a use for a transgenic mouse for evaluating the mutagenic potential of an animal. Again, such a use does not constitute a **specific and substantial** utility within the meaning of 35 U.S.C. 101 because such a use constitutes carrying out further research on the product made, i.e. the transgenic mouse. In other words, the transgenic mouse would be used to quantitate the number of insertion events of the specific system that is constructed, i.e. a particular human L1 retrotransposon element in a specific mouse strain, which constitutes studying the product made, and therefore does not rise to the level of a substantial utility. Thus, one would determine how a human retrotransposon behaves in a mouse, but such a determination does not provide a real world context of use.

At page 8, paragraph 2 of the response, Applicants point to the specification at page 39, beginning at line 7, and assert that the section describes how to use a transgenic mouse comprising a DNAc molecule for identifying an anti-mutagenic compound based on the frequency of retrotransposition in the mouse. However, contrary to Applicants assertion, the cited paragraph does not contemplate that the claimed transgenic mice can be used to identify anti-mutagenic compounds. Furthermore, the specification does not provide specific guidance teaching how to use transgenic mice to identify anti-mutagenic compounds. Thus, the specification fails to enable such a use.

At page 8, paragraph 3 of the response, Applicants point to the specification at page 44, beginning at line 22, and assert that the section describes a system for detecting L1 retrotransposition, which can be used for assessing mutagenic potential, transposition frequency and identification of an anti-mutagenic compound in a transgenic mouse. However, the cited section relates to detecting L1 retrotransposition in cultured cells, but does not describe how to use transgenic mice to identify anti-mutagenic compounds, particularly given that the claimed mice are mosaic for L1 retrotransposition. The cited section does not provide any guidance relating to *in vivo* analysis of retrotransposition events in transgenic mice as claimed. Since the claimed mice would have a germline insertion of an L1 retrotransposon as well as **mosaic** somatic cell genomic insertions that occur during development and post-natally, specific guidance is required for using the transgenic mice to identify anti-mutagenic compounds. It is the role of the specification to provide the specific guidance needed to use the transgenic mouse of the invention.

At page 8, paragraph 2 of the response, Applicants point to the specification at page 53, beginning at line 9, and assert that the section describes the retrotransposon frequency of L1 elements in mouse cells. However, disclosure of the retrotransposition frequency is not sufficient to enable the asserted use of the transgenic mouse, for identifying an anti-mutagenic compound, because the specification lacks sufficient guidance for the *in vivo* analysis necessary to provide an assay for

identifying an anti-mutagenic compound using the claimed transgenic mice, which are necessarily mosaic mutants. Furthermore, disclosure of the retrotransposition frequency is not sufficient to enable the asserted use of the transgenic mouse as a disease model because mice having an appropriate disease-related phenotype are not disclosed, and phenotype is unpredictable, for reasons of record.

For the reasons detailed above, the uses argued by Applicants either do not rise to the level of a specific and substantial utility, and therefore arguments that those uses are enabled are moot, or are not enabled by the instant specification because the specification fails to provide specific guidance teaching how to use the claimed transgenic mouse for those uses.

Therefore, Applicants have not pointed to a specific and substantial utility that is enabled.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER